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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,518	07/08/2003	Jeffrey M. Leiden	104914-159	5333

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/615,518	LEIDEN, JEFFREY M.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/8/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed April 3, 2006 has been entered.

Applicants' election of the species "growth factor" in the response filed April 3, 2006 is acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-36 remain pending in the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-10, 22, and 23 of U.S. Patent No. 6.613,319. Although the

conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are anticipated by Claims 1-10 of U.S. Patent No. 6,613,319.

Claims 24-36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 11-21 and 24 of U.S. Patent No. 6.613,319. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are anticipated by Claims 1-10 of U.S. Patent No. 6,613,319.

Applicant is advised that should Claims 1-11 be found allowable, claims 12-23, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the two claim sets are identical except for the recitation of "the expression vector" recited in Claims 12 and 15. Nevertheless, Claim 12 (and claims depending therefrom) is already limited to the use of a viral vector, as is Claim 1 and claims depending therefrom.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a process for increasing the circulating levels of a self protein in the blood stream of an immunocompetent animal, wherein the method comprises delivering an adenoviral vector *in vivo* to muscle cells of said animal by intramuscular injection in an amount sufficient to obtain expression of and

increase the circulating level of said self protein in the bloodstream of said animal for a period greater than about 30 days, wherein said self protein is erythropoietin or a growth hormone and undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*; and

(ii) a process for increasing the circulating levels of a self protein in the blood stream of an immunocompetent animal, wherein the method comprises transforming muscle cells of said animal *ex vivo* with an adenoviral vector encoding a self protein to thereby produce transformed muscle cells, wherein said self protein is erythropoietin or a growth hormone and undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*; and delivering said transformed muscle cells by intramuscular injection to said animal in an amount sufficient to obtain expression of and increase the circulating level of said self protein in the bloodstream of said animal for a period greater than about 30 days,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are directed to a method for increasing the circulating levels of a self protein in the blood stream of an immunocompetent animal, wherein the method comprises delivering a viral vector *in vivo* to muscle cells of said animal by intramuscular injection in an amount sufficient to obtain expression of and increase the circulating level of said self protein in the bloodstream of said animal for a period greater than about 30 days, wherein said self protein is a polypeptide hormone and undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*.

The specification fails to provide an enabling disclosure for the claimed methods over the full scope because the specification teaches that the only use for the methods are for gene therapy (p. 1, lines 20-22). No other use for the claimed methods are contemplated in the specification. However, the specification does not adequately teach how to use the methods in gene therapy applications. The specification fails to teach any method for transferring any gene into a target cell and expressing that gene

at a therapeutic level in a diseased animal. Thus, the specification does not adequately teach how to use the claimed methods.

The claims encompass methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must teach how to use the claimed methods with specific guidance. However, the specification does not provide any guidance as to the use of the claimed DNA methods to treat a diseased animal. The specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the gene therapy vector required, for treatment of any pathological condition. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods for *in vivo* or *ex vivo* gene therapy. Thus, absent any showing that the claimed methods can be used in gene therapy applications to produce the intended therapeutic effect, the claims directed to methods for gene therapy are not enabled by the disclosure.

The gene therapy art as a whole clearly demonstrates that even in the year 2000, despite intensive effort in every aspect of gene therapy, success in the field was quite limited. Furthermore, Rubanyi et al.

(2001) was published after the effective filing date of this application and reflects essentially the same opinion of those stated in the other references cited regarding the technical barriers and very limited clinical efficacy. The quotes that Applicants refer to describing the optimism in the field of gene therapy is not indicative of enablement at present, but rather suggest that continued effort should result in successful protocols at some time in the future. However, future potential is not sufficient to demonstrate the need for only routine experimentation rather than undue experimentation, given that the art as a whole demonstrates that intensive effort has met with limited success.

The specification fails to provide an enabling disclosure for the method of increasing the circulating level of any gene product in the blood stream of a primate. The guidance and examples provided in the specification are limited to producing elevated levels of erythropoietin (EPO) in the blood stream of a healthy Cynomolgus monkey. Since methods of gene therapy are not routine for the reasons discussed above, undue experimentation would have been required to produce the desired effect using any other gene.

The specification provides examples demonstrating that serum erythropoietin levels and hematocrits are elevated in Cynomolgus monkeys following a single intramuscular injection of an erythropoietin-encoding adenovirus vector (Example 8). An assessment of the safety of the administered adenovirus vector is also described (Example 9). However, none of the examples are directed to applications that result in treatment of a pathological condition in a primate. Moreover, the specification does not offer any guidance in this regard.

Given the limited working examples, the limited guidance in the specification, the broad scope of the claims, and the unpredictability of using the claimed methods in gene therapy applications, undue experimentation would have been required for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-23 are indefinite in their recitation of "the expression vector" because the phrase lacks antecedent basis. See recitation of "the expression vector" in Claims 12 and 15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tripathy et al. (1994) and Dhawan et al. (1991).

The claims are directed to a method for producing increased levels of a circulating gene product in an immunocompetent animal by intramuscular injection of an appropriate expression vector.

Tripathy et al. (1994) disclose stable expression of recombinant EPO in the systemic circulation of CD1 and SCID mice following intramuscular injection of a replication-defective adenovirus vector. Tripathy et al. also suggest using this method in humans (Abstract and p. 11557, column 2, paragraph 2).

Dhawan et al. (1991) disclose that genetically engineered myoblasts comprising a recombinant gene encoding human growth hormone (hGH) and injected into mouse muscle produced detectable levels of hGH in the serum of the mice for 3 months.

Given the suggestion of Tripathy et al. to use the disclosed method to treat human serum protein deficiencies, one skilled in the art would have been motivated to produce similar replication-defective adenovirus vectors to express human EPO or hGH in humans. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have used the claimed method in humans to increase the circulating level of the vector-encoded gene product in the blood stream.

One would have been motivated to have combined the teachings of Tripathy et al. and Dhawan et al. to express either human EPO or hGH in humans.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history

information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER